293
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant: M. Rigdon Lentz

Serial No.: 09/083,307 Art Unit: 3835

Filed: May 22, 1998 Examiner: P. Bianco

For: *METHOD AND COMPOSITIONS FOR TREATMENT OF CANCERS*

United States Patent and Trademark Office
Washington, D.C. 20231

APPEAL BRIEF

Dear Sir:

This is an appeal from the Office Action mailed October 21, 2002, finally rejecting claims 1-23. A Notice of Appeal was filed on October 25, 2002. The appropriate fee for filing of the Appeal Brief and a Petition for an Extension of Time for one month, up to and including January 25, 2003, and the appropriate fee for a small entity, accompanies this Appeal Brief along with an Amendment to the Claims.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is M. Rigdon Lentz.

(2) RELATED APPEALS AND INTERFERENCES

This case corresponds to Appeal No. 2001-2168 decided February 12, 2002.

In this decision, the Board affirmed rejections of claims 1-4, 8, 9, 16, 18-20, and 22 over Lentz, claim 21 over Lentz in combination with Okarma, claim 7 over Lentz in view of Chen, and claim 5, 6, 10-15, 17 and 23 over Lentz in combination with Wolfpe under 35 U.S.C. 103, and newly rejected claims 10-15, 17, 21, and 23 under 37 C.F.R. 1.196(b). The Decision at page 21 states in relevant part **"we herewith designate our affirmance of all of the examiner's rejections as new grounds of rejection under 37 CFR § 1.96(b)."** Since the examiner failed to address any of these rejections in the Office Action mailed October 21, 2002, nor appellant's response filed April 12, 2002, these issues are treated again on appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-23 are pending and rejected prior to entry of the accompanying Amendment. The text of each claim on appeal, as pending and as proposed to be amended, is set forth in the Appendix to this Appeal Brief.

Following entry of the amendment, claims 16 and 21 will have been cancelled and claims 1-15, 17-20, 22 and 23 will be pending.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment under 37 C.F.R. 1.196(b) mailed April 12, 2002. An Amendment accompanies this Appeal Brief.

(5) SUMMARY OF THE INVENTION

The invention is the discovery that one can use a filter to selectively remove molecules of less than 120,000 daltons from the blood of a patient and induce remission in a cancer or other type of chronic disease, and that this process, in combination with certain adjuvant therapies, can not only induce a remission, but maintain the patient in remission. [Page 2, line 27 to page 3, line 27]. The filtration process removes material which is apparently produced by the cancer to prevent the patient from killing the tumors. The adjunct therapy is typically treatment with an anti-angiogenic compound, treatment with one or more cytokines, or a procoagulant compound, although it may be more conventional chemotherapy or radiation (page 3, lines 7-17).

The examples demonstrate that the method was effective in treating cancer patients. The first example at pages 12-13, was a lung cancer patient who had failed conventional chemotherapy. Filtration alone reduced the tumor size and number. The second example at page 13 described a woman with metastatic breast cancer who had failed radiation and conventional chemotherapy. Filtration was used to enhance immune attack on the tumors (leading to inflammation, see page 13, lines 12-16), then thalidomide, an anti-angiogenic compound, used to further resolve the tumors. Example three at pages 13-14 was a patient with metastatic melanoma who was treated initially with filtration to induce tumor inflammation, then treated with thalidomide to induce remission. Example 4 at page 14 is a patient with metastatic adenocarcinoma who had failed treatment with taxol, ciplatin and etoposide. The filtration was used to cause tumor inflammation, then followed with thalidomide to cause further tumor regression.

(6) ISSUES ON APPEAL

The following issues are presented on appeal:

(1) Whether claims 1-4, 8, 9, 16, 18-20 and 22 are obvious under 35 U.S.C. 103 over U.S. Patent No. 4,708,713 to Lentz;

(2) Whether claim 7 is obvious over U.S. Patent No. 4,708,713 to Lentz in view of Chen, et al., J. Neuropathology and Experimental Neurology, pp. 541-550 (May 1997);

(3) Whether claims 5, 6, 10-15, 17 and 23 are obvious over Lentz in combination with U.S. Patent No. 5,861,483 to Wolpe;

(4) Whether claims 10-15, 17, and 23, excluding the term "radiation", are indefinite under 35 U.S.C. 112, second paragraph;

(5) Whether claims 10-15, 17, and 23 are based upon an enabling disclosure as required by 35 U.S.C. 112, first paragraph.

(7) GROUPING OF THE CLAIMS

The claims do not stand or fall together, as discussed below.

(8) ARGUMENTS

(a) <u>The Invention</u>

There are multiple inventions described in this application. The first is that the prior art ultrafiltration process, the subject of U.S. Patent No. 4,708,713, or a filter having a lower molecular weight cutoff, as discussed above, can be used in combination with other agents, where the ultrafiltration induces remission, and the other agents maintain the patient in remission

(claims 9-23, limited to the lower molecular weight filter). The second invention, which is the invention claimed in this pending application, and the specific device defined by claims 1-9, is the discovery that one can use a filter to selectively remove molecules of less than 120,000 daltons from the blood of a patient, not including immunoglobulin G, and induce remission in a cancer or other type of chronic disease. The filtration process removes material which is apparently produced by the cancer to prevent the patient from killing the tumors.

The examples demonstrate that the adjunctive method was effective in treating cancer patients. The first example at pages 12-13, was a lung cancer patient who had failed conventional chemotherapy. Filtration alone reduced the tumor size and number. The second example at page 13 described a woman with metastatic breast cancer who had failed radiation and conventional chemotherapy. Filtration was used to enhance immune attack on the tumors (leading to inflammation, see page 13, lines 12-16), then thalidomide, an anti-angiogenic compound, used to further resolve the tumors. Example three at pages 13-14 was a patient with metastatic melanoma who was treated initially with filtration to induce tumor inflammation, then treated with thalidomide to induce remission. Example 4 at page 14 is a patient with metastatic adenocarcinoma who had failed treatment with taxol, ciplatin and etoposide. The filtration was used to cause tumor inflammation, then followed with thalidomide to cause further tumor regression.

(b) Prior Art Rejections under 35 U.S.C. 103

The Filter Size of the Lentz Patent and the Present Application are Different

One of the questions raised at the Board of Appeals hearing (which had not previously been raised by the examiner) was exactly what filter was used in the examples. Dr. Lenz stated that the filters were filtration devices similar to those used for kidney dialysis, but modified as to the pore size to have a cutoff of approximately 120,000 daltons, so that the immunoglobulins (IgM, IgG) would be retained and given back to the patient, both so that they would not have to be replaced which is expensive but also because the patient's own immunoglobulin was believed to enhance the immune reaction against the tumor cells.

One of the other issues raised at the Board of Appeals hearing was how the prior art filter described in U.S. Patent No. 4,708,713 to Lentz could have such similar parameters to the parameters of the claimed filters, yet have different molecular weight cutoffs. The Board states beginning on page 6, "a suitable filter having a molecular weight cutoff of 120,000 daltons or less will have a pore size of 0.03 microns and a thickness of less than 25 microns and preferably less than 10 microns." (referring to page 4, lines 19-23). However, the application also states that the sieving coefficient should be between 10 and 30%, for this pore size to have the desired cutoff. The application further states that if the filter is a capillary membrane filter it should have a pore size between 0.02 and 0.05 microns, and that it should have a pore size of between 0.04 and 0.08 microns if it is a parallel plate filter (page 4, lines 12-16). More relevantly, the patent application states "The actual pore size that yields the desired cutoff of approximately 120,000 daltons is determined based on the fluid flow geometry, shear forces, flow rates, and surface area" (page 4, lines 16-19).

In contrast, the Lentz patent says at col. 4, lines 2-6, "The blood fraction having low molecular weight components, e.g. those having molecular weight less than about 1,000,000 Daltons, preferably less than about 200,000 Daltons, passes through the membrane..." and at col. 4, lines 56-68, "The ultrafilter medium or membrane should have an effective pore size less than about 15 microns in diameter in order to selectively separate the desired low molecular weight components from the blood. A filter media having an effective pore size of about 0.03-0.07 microns will separate components with molecular weight less than about 200,000 Daltons. A membrane with an effective pore size less than about 0.03 micron is needed to separate blood components with molecular weights less than about 30,000 Daltons." Further, the patent states at col. 5, the various other factors to adjust: flow rate, differential pressure and membrane thickness.

Accordingly, looking solely at pore size, the Lentz patent states the following:

Lentz Patent		Lentz patent application	
pore size	molecular weight cutoff	pore size	molecular weight cutoff
0.07-0.1 microns	1,000,000		
0.03-0.07 microns	200,000		
		0.03 microns	120,000
		0.02 and 0.05 microns	120,000
		0.04 and 0.08 microns	120,000
< 0.03 microns	30,000		

There is nothing inconsistent between the patent and the patent application, as this comparison shows. As Dr. Lentz stated at the hearing, and which is further supported by the materials submitted with the response under 37 C.F.R. 1.196(b) ("Filtration Fundamentals: Is Knowledge of Filter Technology Something You Let Fall Through the Cracks?" by Bob Sinclair, The Scientist 12(19):18 (September 1998); "Laboratory Filtration Concepts" by Pall Live Sciences), it is well known that *pore size is only one factor determining molecular weight cutoff of a filter.* One cannot compare only the pore sizes of two different filters to determine the molecular weight cutoff. The materials the filters are made of, the thickness of the filter, the shear rates, the surface configurations, the materials to be separated, the flow rates, and many other variables determine the actual molecular weight cutoff. Therefore one *cannot* say that

because the Lentz patent recites a range of pore sizes and the present application recites a similar range of pore sizes, that they will have the same molecular weight cutoffs.

The only way to actually compare cutoffs is to read the Lentz patent and compare what it teaches with the teachings of the present application. Lentz discloses using a filter to remove all blood components of 200,000 mw or less to treat cancer patients (see col. 6, lines 34-46). While favorable results were obtained, the patient loses all of the IgM, IgG and IgA antibodies which have a molecular weight greater than 120,000, but less than 200,000 daltons (as shown by the excerpt from "General Immunology" by Herman N. Eisen, page 78), which are extremely important to fight infection. Since infection is a major problem for cancer patients, this method would not have been developed if the patentee had believed that one did not have to remove the immunoglobulins. However, it simply had not been determined even as of the issue date of the '713 patent (1987), what component(s) was being removed by the procedure, which allowed the patient to then fight off the cancer.

As Dr. Lentz further explained at the Board hearing, it has taken years of subsequent work to determine that the "bad" component which is removed by the procedure is a relatively low molecular weight component, allowing the substitution of a filter with a lower molecular weight cutoff. The Lenz patent speculates at col. 6, lines 39-46, that it is a component of a similar weight to an immunoglobulin which protected the tumor; col. 4, lines 65-68, lead one to believe that it is a component of less than 30,000 which is the tumor protective agent. In fact, as Dr. Lentz has subsequently learned, it is neither, but the soluble tumor necrosis receptor

fragments secreted by the tumor that protects the tumor. The size of these fragments are approximately 55,000 and 75,000 daltons (see, U.S. Patent No. 6,231,536 and Ammirato, et al., Front. Biosci. 1:6:B17-24(2001). See also Selinsky, et al., Immunology 94:88-91 (1998)).

In summary, the evidence strongly supports the conclusion that the filter of the Lentz patent is ***not*** inherently the same as the claimed filter. The Lentz patent explicitly teaches that the filter must remove a complex that is approximately 120,000 daltons. The claimed application explicitly requires that the filter ***not*** remove molecules having molecular weights of approximately 120,000 daltons. The pore sizes, as well as the other features of the filters described in the Lentz patent and the present application, are ***not*** overlapping, but indicate that there are ranges of pore sizes that will result in different molecular weight cutoffs, depending on the filter construction. The evidence now before the Board supports the statements that have been made in the application and during prosecution in this regard.

In summary, Lentz does not disclose the selection and use of a filter that removes components having a molecular weight of 120,000 daltons or less from the blood of a patient (claims 1, 2, 3, 4), nor a system utilizing such a filter (claim 9). No prior art has even been cited as showing filters with a different pore sizes or geometries for staggered removal of materials from the blood (claim 20).

There is no Motivation to Combine Ultrafiltration with other Treatments

There is no disclosure of combining filtration with other methods to induce further remission or maintain remission. The patients that are described in the examples had *previously*

been treated with every other type of treatment, and had failed those treatments. They had been treated with chemotherapy and with radiation and their cancers continued to grow and destroy their bodies. Nothing has been cited that would lead one skilled in the art to say "yes, these treatments all failed before, but now that ultrafiltration has caused the tumors to shrink in size, now we should use these other treatments again, and they will be expected to work." This is absurd. One skilled in the art would say that once a patient has "failed" a therapy – i.e., their cancer has failed to respond to the treatment, there is absolutely no motivation to think the cancer might suddenly become susceptible to the treatment.

See, for example page 12, lines 25-29, "These tumors had also failed methotrexate, adriamycin, ifosphomide, and dactinomycin." See, for example, page 13, lines 6-9, "Mrs. J.R. is a 44 year old lady who had metastatic breast cancer that had failed radiation therapy and treatment with chemotherapeutic agents: cytoxan, adriamyxin, 5-FU, taxol, cis-platin, navalbine, tamoxifin and arimedex." See, further page 14, lines 8-11, "His tumors had failed to respond to taxol, cis-platin and etoposide."

This evidence totally teaches away from any such treatment. Yet these exact same patients, all of whom responded to the ultrapheresis, showed further tumor reduction following adjunct treatment. For example, page 14, lines 15-18, "There was a 50% reduction in the primary tumor in the lung and liver. Thalidomide was then started at 200 mg each night. One month later, the scans revealed further reduction in the tumors in the lung and liver. The patient's pains have all been resolved and he is asymptomatic at this time."

Note, these examples demonstrate that ultrapheresis was effective even when the patient had failed chemotherapy, including with antiangiogenic compounds, as well as radiation. Moreover, the examples demonstrate that even further benefit could be achieved by then treating the patients with chemotherapeutic agents even though they had previously failed treatment with chemotherapeutic agents. Nothing in any of the cited art could possibly lead one skilled in the art to such an outcome.

Moreover, in response to the Board's statement that appellant does not show an effect greater than what is considered to be the closest prior art, this is clearly wrong.

The examples all start with treatment using ultrapheresis. Regardless of whether or not there is a difference in tumor reduction due to the molecular weight cutoff (impossible to tell, since each patient responds differently and it would be unethical to treat a human patient first with one filter, and then the second having a lower molecular weight cutoff), the principle difference based on the molecular weights is that one has to treat patients in the first case with whole plasma to restore their immunoglobulins (the issue regarding non-obviousness is that one could not predict treatment with the lower molecular weight cutoff would be efficacious; not whether or not it produced better or different results). This supplementation is extremely expensive. What is significant, and extremely unexpected, is that further tumor reductions were then observed when the patient was treated with a chemotherapeutic agent. As discussed above, these patients had all failed treatments with chemotherapeutic agents. There was absolutely no

reason to believe they would be responsive, in fact conventional wisdom would lead one skilled in the art to believe they would *not* be responsive.

Chen teaches that soluble TNF-alpha receptors suppress the patients ability to fight cancers. Soluble TNF-alpha receptors are 55,000 and 75,000 daltons in size (page 541, col. 1). Contrary to the Board's opinion, Chen does not teach that one could remove the soluble TNF-alpha receptors and that would reduce the tumors.

If it were so obvious that one could just remove the soluble TNRFs, then one can be certain that Chen would have suggested do so. Instead, Chen is making an observation that would lead one skilled in the art to believe that sTNFRs must be part of a much more complex situation. *Chen is not a study in humans or even tumors, but a study of cell-cell interaction in cell culture.* It is well known that cell culture is not predictive of what might occur in a patient, but in this case, the sTNFRs are not even removed from the cell culture, they are merely measured and found to be released by the cells. It is speculated that the factors may play a role "These data suggest that soluble TNF receptors may play a role in the mechanism by which malignant gliomas downregulate the effects of infiltrating immune-competent cells."

This is NOT a teaching that tumors release these factors; that these factors play a physiological role; nor that altering their levels would have any significance in a patient.

The Board decision totally ignores its own standards in reaching such a conclusion. It leaps from a study that says tumor cells in culture produce soluble TNFRs that *"may play a role in the mechanism by which malignant gliomas downregulate the effects of infiltrating immune-*

competent cells." to the conclusion that removal of sTNFs using ultrafiltration will cause tumor reduction in patients, even when the tumors have metastasized throughout the body and failed all accepted chemotherapy and radiation therapy. Such a conclusion defies common sense, much less the law.

Therefore the combination of Lentz with Chen is **not** the same as what appellant is claiming. Moreover, there is nothing that would lead one to believe that only the smaller molecular weight molecules could be removed and the cancer be treated effectively, based on Lentz. Accordingly, one skilled in the art would be led **away** from the combination of Lentz and Chen, **not** to a **modified combination**.

It is not clear if the claims pending have also been rejected over Okarma, et al. In the event that the claims have been rejected over Okarma alone or in combination with Lentz, it is noted that Okarma, et al., describes removal of cytokines *and other factors* using silica to absorb the materials. Lentz describes removal of factors based on molecular weight. Okarma, et al. does something different: He removes factors of all molecular weights based on binding to silica-based absorbents.

There is nothing that would lead one to combine Okarma, et al., with Lentz, modify Lentz to remove lower molecular weight blood components (i.e., molecular weights 120,000 daltons or less rather than 200,000 daltons), modify Okarma et al., to leave in the cytokines (and everything else bound by silica but which is less than 120,000 daltons) but remove the cytokine inhibitors removed by ultrafiltration, and have any expectation of success.

Wolpe states that certain factors are known which enhance the immune system. Wolpe does not address the issue of whether or not there is an immunosuppressive component having a molecular weight in the critical range between that which is now claimed and that which is taught in the thirteen year old patent to Lentz, prior to many subsequent studies which were required to determine that the immunosuppressive element does **not have a molecular weight similar to that of an immunoglobulin or immunoglobulin complex.** The difference is important: by using the lower molecular weight cutoff, the patient can keep their own immunoglobulin, helping them to more successfully fight off infection.

In summary, the art in combination does not make obvious the method of claims 5, 6, 7, and 8, nor the system of claims 10-15 and 17. No prior art has even been cited which discloses the use of a procoagulant compound (claim 11) or chemotherapeutic agent (claims 14 and 15).

The Board's previous statements with regard to the number of patients treated, and lack of published evidence, on page 16, is totally inappropriate and unsupported in the law. There is no legal requirement to say how many patients have been treated in order for comparative results to be credible. Indeed, there is no legal requirement for any patients to have been treated. This is not an FDA approved treatment. Each one of these patients was treated following review by an independent hospital review board which grants a compassionate use of the procedure solely after review of the individual patient's records. Appellant has not yet obtained the financial resources to conduct large scale clinical trials which will cost millions of dollars to obtain approval. Appellant has conducted further clinical trials in Europe at the Klinik-At-Georg and

has data showing efficacy in a number of patients, with the following results: 50% or greater tumor reductions were observed in 4/4 patients with metastatic breast cancer, 2 of 2 patients with metastatic prostate cancer, 1 of 1 patient with metastatic colon cancer, and 1 of 1 patient with metastatic non-small cell carcinoma of the lung. These patients were treated using a Sepharose column having coupled thereon rabbit polyclonal antibody to human sTNFR1 and sTNFR2. U.S. Patent No. 6,379,708, which claims the same subject matter as claims 6, 7, 12, 13, and 17 is noted as further evidence of enablement and patentability of the claims under 35 U.S.C. 112.

The court stated in *In re Brana*, "Usefulness in patent law and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *In re Brana*, 51 F.3d 1560, 1568 (Fed.Cir. 1995). The law is explicitly clear, however, as to what pharmaceutical utility does **not** require. Pharmaceutical utility does not require human testing (*In re Jolles*, 628 F.2d 1322 (CCPA, 1980); *In re Krimmel*, 292 F.2d 948 CCPA, 1961); *Cross v. Iizuka*, 753 F.2d 1040 (1985); and *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995)) or animal testing (*In re Krimmel*, 292 F.2d 948 CCPA, 1961) and *Cross v. Iizuka*, 753 F.2d 1040 (1985)). Pharmaceutical utility does not require a showing of therapeutic safety (*In re Brana* 51 F.3d 1560 (Fed. Cir. 1995) and *In re Irons*, 340 F.2d 974, 978 (CCPA 1965)), and it most certainly does not require a showing of efficacy (See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); Ex parte *Jovanovics, 211*

USPQ 907 (Bd. Pat. App. & Inter. 1981)). The reasons for this are policy based because it is in the best interest of the public, the benefactors of the inventive material, to have the choice of when, how, and why to use the disclosed material (*In re Brana*, 51 F.3d 1560, 1568 (Fed.Cir. 1995) Not only does the public lose because of lost opportunity to utilize the invention, the public loses because of lost opportunity to benefit from further pharmaceutical research. Commenting on why the utility standard is what it is the *Brana* court stated, "Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many areas such as the treatment of cancer.").

(c) **Rejections under 35 U.S.C. 112**

Claims 10-15, 17 and 23 were rejected under 35 U.S.C. 112 on the basis that the specification is allegedly non-enabling for inclusion of the term "radiation" and that inclusion of "radiation" into a claim to a kit was indefinite.

Rejection of Claim 17

Claim 17 was rejected on the basis that the Board did not understand how a kit could include radiation. The claim has been amended in the accompanying amendment to delete the reference to radiation, and claim 16 cancelled, solely to facilitate prosecution. The claims were also amended to define a system rather than a kit. The treatment of patients with radiation is well known. Hospitals have the equipment to treat patients with radiation along with ultrapheresis. Therefore claims to a system including both ultrapheresis and radiation are enabled and one skilled in the art would be able to practice the claimed method.

Rejection of Claim 21

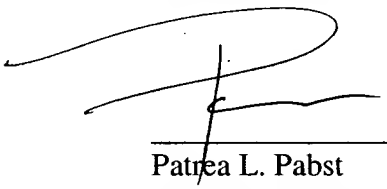
Claim 21 was rejected as unsupported by the specification as filed. This claim has been cancelled in the accompanying amendment solely to facilitate prosecution.

(9) Summary and Conclusions

Claims 1-15, 17-20, 22, and 23, are not obvious over the prior art, alone or in combination. The prior art fails to provide any motivation to selectively remove components having a molecular weight of 120,000 daltons or less, much less in combination with selective removal of compounds such as cytokine or soluble cytokine receptors, and even less so in

combination with known therapies for the treatment of patients who had already failed these treatments alone. There is no disclosure of the motivation to combine, much less so any reasonable expectation of success. The claims are definite with respect to the term "radiation" or in the alternative, this issue has been mooted by entry of the accompanying amendment.

Respectfully submitted,



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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this Appeal Brief, together with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, P. O. Box 2327, Arlington, VA 22202

Jean Hicks

Date: January 27, 2003

APPENDIX: Claims as pending prior to entry of Amendment

1. A method for inducing an immune response against transformed, infected or diseased tissue comprising

removing only components present in the blood having a molecular weight of 120,000 daltons or less, until the transformed, infected, or diseased tissue is reduced in amount.

2. The method of claim 1 wherein the tissue is a solid tumor.

3. The method of claim 1 wherein the components are removed from one blood volume.

4. The method of claim 1 wherein the components are removed in multiple treatments.

5. The method of claim 1 further comprising treating the tissue with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation.

6. The method of claim 5 wherein the agent is a cytokine and the cytokine is selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

7. The method of claim 1 further comprising selectively removing soluble TNF receptor 1 and receptor 2 molecules.

8. The method of claim 1 further comprising vaccinating the patient with a vaccine against the transformed, infected or diseased tissue, wherein the vaccine is produced by immunization with antigens unique to the transformed, infected or diseased tissue.

9. A system for inducing an immune response against transformed, infected or diseased tissue comprising

a device for removing only components present in the blood having a molecular weight of 120,000 daltons or less, having inlet and outlet means for connection to a pump and tubing to recirculate the blood of a patient through the device.

10. The kit of claim 17 wherein the agent is an anti-angiogenic compound.

11. The kit of claim 17 wherein the agent is a procoagulant compound.

12. The kit of claim 17 wherein the agent is a cytokine.

13. The kit of claim 12 wherein the agent is a cytokine and the cytokine is selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

14. The kit of claim 17 wherein the agent is a chemotherapeutic agent.

15. The kit of claim 14 wherein the agent is selected from the group consisting of alkylating agents, doxyrubicin, carboplatinum, cisplatinum, and taxol.

16. The system of claim 9 wherein the system includes means for administering radiation to the tissue.

17. A kit for treatment of a patient to induce an immune response against transformed, infected or diseased tissue comprising:

(a) a device for removing only components present in the blood having a molecular weight of 120,000 daltons or less, and

(b) an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation, in a dosage

formulation for treatment of the patient in combination with treatment of the patient with the device to remove blood components having a molecular weight of 120,000 daltons or less.

18. The system of claim 9 wherein the device is a capillary membrane filter with a pore size of between about 0.02 and 0.05 microns.

19. The system of claim 9 wherein the device is a parallel plate filter with a pore size of between about 0.04 and 0.08 microns.

20. The system of claim 9 wherein the device comprises filters with different pore sizes or geometries to provide for staggered removal of materials from the blood.

21. The system of claim 9 wherein the device is an absorbent column selectively removing specific cytokine or cellular inhibitors from the blood.

22. The system of claim 9 wherein the blood is plasma.

23. The kit of claim 17 further comprising anticoagulant to treat the device for removal of components from the blood prior to use.

APPENDIX: Clean copy of claims as amended in accompany Amendment

1. (twice amended) A method for inducing an immune response against transformed, infected or diseased tissue in a patient comprising

treating the blood of the patient to remove the components present in the blood having a molecular weight of 120,000 daltons or less, and not the majority of the immunoglobulin G, until the transformed, infected, or diseased tissue is reduced in amount.

2. The method of claim 1 wherein the tissue is a solid tumor.

3. The method of claim 1 wherein the components are removed from one blood volume.

4. The method of claim 1 wherein the components are removed in multiple treatments.

5. The method of claim 1 further comprising treating the tissue with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation.

6. The method of claim 5 wherein the agent is a cytokine and the cytokine is selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

7. The method of claim 1 further comprising selectively removing soluble TNF receptor 1 and receptor 2 molecules.

8. The method of claim 1 further comprising vaccinating the patient with a vaccine against the transformed, infected or diseased tissue, wherein the vaccine is produced by immunization with antigens unique to the transformed, infected or diseased tissue.

9. (twice amended) A system for inducing an immune response against transformed, infected or diseased tissue in a patient comprising

a device for removing only components present in the blood having a molecular weight of 120,000 daltons or less, and not the majority of the immunoglobulin G, having inlet and outlet means for connection to a pump and tubing to recirculate the blood of a patient through the device.

10. (amended) The system of claim 17 wherein the agent is an anti-angiogenic compound.

11. (amended) The system of claim 17 wherein the agent is a procoagulant compound.

12. (amended) The system of claim 17 wherein the agent is a cytokine.

13. (amended) The system of claim 12 wherein the agent is a cytokine and the cytokine is selected from the group consisting of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

14. (amended) The system of claim 17 wherein the agent is a chemotherapeutic agent.

15. (amended) The system of claim 14 wherein the agent is selected from the group consisting of alkylating agents, doxyrubicin, carboplatinum, cisplatinum, and taxol.

17. (twice amended) A system for treatment of a patient to induce an immune response against transformed, infected or diseased tissue comprising:

(a) a device for removing only components present in the blood having a molecular weight of 120,000 daltons or less, and not the majority of the immunoglobulin G, and

(b) an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, and chemotherapeutic agents[, and radiation], in a dosage formulation for treatment of the patient in combination with treatment of the patient with the device to remove blood components having a molecular weight of 120,000 daltons or less.

18. The system of claim 9 wherein the device is a capillary membrane filter with a pore size of between about 0.02 and 0.05 microns.

19. The system of claim 9 wherein the device is a parallel plate filter with a pore size of between about 0.04 and 0.08 microns.

20. The system of claim 9 wherein the device comprises filters with different pore sizes or geometries to provide for staggered removal of materials from the blood.

22. The system of claim 9 wherein the blood is plasma.

23. (amended) The system of claim 17 further comprising anticoagulant to treat the device for removal of components from the blood prior to use.

TABLE OF CONTENTS